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Critical Review

Management of Borderline Resectable Pancreatic Cancer

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With the rapid development of imaging modalities and surgical techniques, the clinical entity representing tumors that are intermediate between resectable and unresectable pancreatic adenocarcinoma has been identified has been termed "borderline resectable" (BR). These tumors are generally amenable for resection but portend an increased risk for positive margins after surgery and commonly necessitate vascular resection and reconstruction. Although there is a lack of consensus regarding the appropriate definition of what constitutes a BR pancreatic tumor, it has been demonstrated that this intermediate category carries a particular prognosis that is in between resectable and unresectable disease. In order to downstage the tumor and increase the probability of clear surgical margins, neoadjuvant therapy is being increasingly utilized and studied. There is a lack of high-level evidence to establish the optimal treatment regimen for BR tumors. When resection with negative margins is achieved after neoadjuvant therapy, the prognosis for BR tumors approaches and even exceeds that for resectable disease. This review presents the current definitions, different treatment approaches, and the clinical outcomes of BR pancreatic cancer.

Introduction

Pancreatic cancer is the third-leading cause of cancer-related death and has been estimated to be the second by 2030, second only to lung cancer, with a predicted mortality of 43,090 deaths in 2017 in the United States (1, 2). Surgical resection remains the primary curative option for patients with pancreatic cancer, although only 15% to 20% will present with initially resectable disease. The overall survival (OS) for patients with margin-negative resection has been ~20% at 5 years (3). However, for those with positive surgical margins (R1 or R2), OS has been much poorer, approaching the survival of patients with locally advanced, unresectable pancreatic cancer (4-6). Thus, selecting the appropriate patients for surgical resection is critical to optimizing the treatment outcomes and minimizing the risk of undue treatment morbidity for patients unlikely to benefit.

A number of definitions of resectability have been proposed using radiographic imaging of tumor involvement of the

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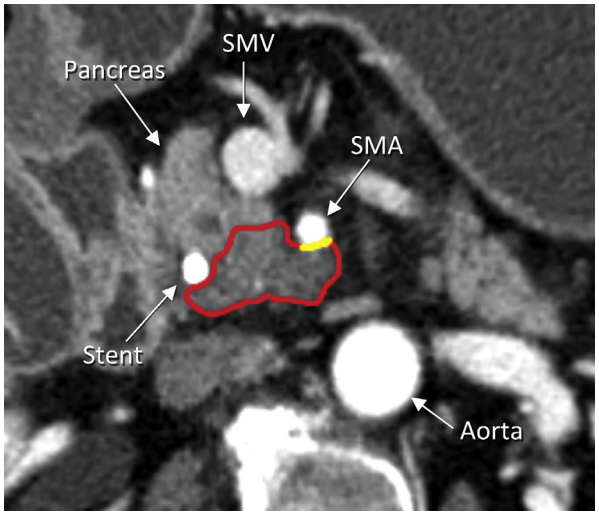

Fig. 1. Magnified section of a computed tomography axial slice of a borderline resectable pancreatic adenocarcinoma (red contour) highlighting the tumor contact region with the superior mesenteric artery (SMA; yellow contour) <180°. *Abbreviation:* SMV = superior mesenteric vein. (A color version of this figure is available at www.redjournal.org)

surrounding vasculature. Historically, any tumor abutment along the superior mesenteric artery or celiac axis rendered tumors unresectable. However, improvements in multidetector computed tomography (CT), with protocols optimized for pancreatic cancer imaging offer higher resolution images of the tumor–vessel interface (7-9), which has allowed improved evaluation of the degree of abutment and encasement of adjacent vessels. Tumors demonstrating only a limited amount of arterial involvement, previously not considered good candidates for resection, are now being designated potentially resectable, also termed "borderline resectable" (BR), tumors that could eventually be resected after sufficient downstaging and/or with a more aggressive surgical approach (Fig. 1).

The current strategy, therefore, has been to apply a multimodality approach, usually consisting of neoadjuvant systemic therapy with or without the use of radiation therapy (RT) to "sterilize" the tumor boundaries in contact with peripancreatic vessels and allow for successful margin-negative resection (10-12).

The present report aimed to provide a critical review of the different approaches for the management of BR pancreatic ductal adenocarcinoma (PDAC), specifically addressing the different definitions of BR disease and exploring the current treatment modalities in depth.

Definition of BR pancreatic cancer

Localized PDAC has been classified into 3 categories—early/resectable, BR, and locally advanced/unresectable disease. However, just what constitutes a BR case is subjective, and many definitions have been proposed. Mehta et al (13) were among the first to describe patients with "marginally resectable" pancreatic cancer, intermediate between resectable and unresectable disease, as a group of patients who had potentially resectable disease after preoperative chemoradiation therapy. Since then, many different classifications to categorize tumor resectability have been created, assessing both arterial and venous involvement (14-20), while others have specifically examined the tumor interface with the portal vein (PV) and superior mesenteric vein (SMV) (21, 22).

Currently, 3 systems have been proposed to define PDAC resectability that have been more widely adopted: the MD Anderson Cancer Center (MDACC) (14), the Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary

Table 1 Different definitions of borderline resectable pancreatic cancer

Vessel	MDACC	AHPBA/SSO/SSAT	NCCN
CA	No contact	No contact	Pancreatic body/tail: solid tumor contact ≤180° or >180° without involvement of aorta or gastroduodenal artery
CHA	Short-segment encasement/abutment	Abutment or short segment encasement	Pancreatic head: solid tumor contact without extension to CA or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction
SMA	Tumor abutment ≤180°	Tumor abutment ≤180°	Pancreatic head: solid tumor contact ≤180°
SMV/PV	Short-segment occlusion amenable to resection and reconstruction	Abutment with or without impingement; or encasement but without encasement of nearby arteries; or short-segment occlusion amenable to resection and reconstruction	Solid tumor contact >180° or ≤180° with contour irregularity or vein thrombosis but with suitable vessel proximally and distally to site of involvement, allowing for safe and complete resection and vein reconstruction*

Abbreviations: AHPBA/SSO/SSAT = Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; CA = celiac axis; CHA = common hepatic artery; MDACC = MD Anderson Cancer Center; NCCN = National Comprehensive Cancer Network; PV = portal vein; SMA = superior mesenteric artery; SMV = superior mesenteric vein.

* The most recent version of the NCCN resectability criteria also considers cases with solid tumor contact with the inferior vena cava as borderline resectable.

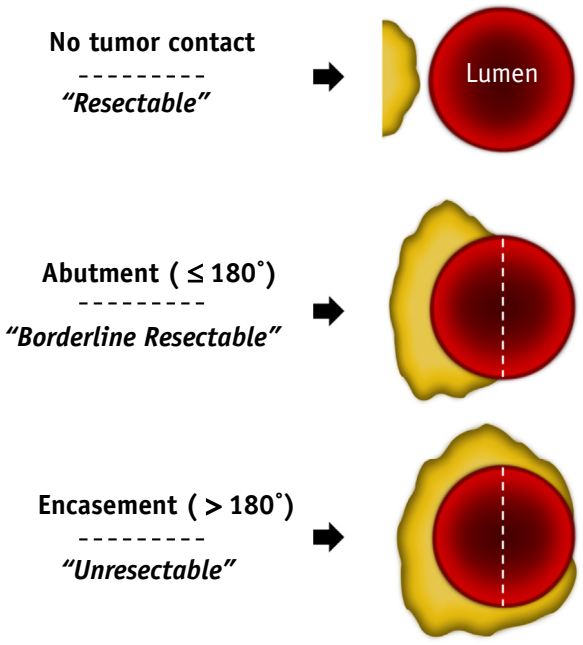

Fig. 2. Common tumor–vessel attributions of patients considered "resectable," "borderline resectable," and "unresectable" according to tumor involvement of major peripancreatic arteries. Artery representation shown in axial slice view. Dark yellow represent the tumor. (A color version of this figure is available at www.redjournal.org.)

Tract (AHPBA/SSO/SSAT) (15, 16), and the National Comprehensive Cancer Network (NCCN) (17) definitions (Table 1). The term "abutment" generally indicates $\leq$180° of solid tumor contact around the vessel on an axial section, and the term "encasement" implies >180° of tumor involvement around the vessel (Fig. 2).

Slight differences exist among these 3 systems regarding arterial involvement, with celiac axis (CA) contact rendering pancreatic tumors unresectable per the AHPBA/SSO/SSAT and MDACC criteria and the latest version of the NCCN criteria considering tumors of the pancreatic body with solid tumor contact with the CA of $\leq$180° or >180° without involvement of aorta or the gastroduodenal artery as BR, because these tumors could be resected using a modified Appleby procedure (distal subtotal pancreatectomy with resection of the celiac axis but preservation of the hepatic and gastric perfusion through retrograde flow in the gastroduodenal artery). Discrepancies are also present among the different criteria in relation to venous involvement. The AHPBA/SSO/SSAT criteria include cases demonstrating abutment (with or without impingement) or encasement of the PV or SMV in the BR category. In contrast, these cases would be considered resectable using the MDACC criteria, as long as no venous occlusion is present. Both systems consider PV short-segment occlusion amenable to resection and reconstruction as BR disease. The different definitions of BR disease according to these 3 systems are shown in Figure 3.

In the latest version of the resectability criteria proposed by the NCCN (17), the panelists reinforced the use of radiology reporting templates, such as the one suggested by the Society of Abdominal Radiology and the American Pancreatic Association (23), using the degree of tumor involvement around the respective vessels (<180° or $\geq$180°) rather than words to describe it to reduce subjectivity and facilitate comparisons among future studies.

Treatment of BR disease

Tumors classified as BR, although potentially resectable, have a greater risk of a positive margin after surgery and could require vascular resection and reconstruction (24). In addition, these tumors harbor an increased risk of rapid systemic subclinical spread and subsequent early progression after therapy. One hypothesis is that the close contact with adjacent vasculature facilitates the occurrence of extrapancreatic perineural invasion, consequently leading to early systemic spread of disease and decreased survival after pancreaticoduodenectomy (PD) (25).

Therefore, interest has been increasing in using neoadjuvant therapy for BR cases (26). The advantages of this strategy include possible tumor downstaging to reduce the degree of vessel abutment, sterilization of the periphery of the lesion to increase the likelihood of margin-negative resection, and, most importantly, the identification of patients with biologically more indolent disease who will not develop progression during the neoadjuvant therapy period (5, 6, 27). In the ESPAC-4 trial, gemcitabine plus capecitabine demonstrated superiority compared with gemcitabine alone for patients who had undergone complete macroscopic resection (R0 or R1) for PDAC. However, 60% of patients had positive resection margins, suggesting that a large number had BR disease. In addition, a subgroup analysis showed that those with positive margins did not benefit from intensifying chemotherapy, offering the rationale for the delivery of neoadjuvant therapy for cases with a greater probability of positive margins after surgery (28). Although current consensus guidelines have recommended the use of neoadjuvant therapy before surgical resection of BR disease, the data are insufficient to recommend a standard treatment regimen (17, 20, 29, 30).

Neoadjuvant chemoradiation therapy

The reported resectability rates after neoadjuvant chemoradiation therapy have varied, with some studies demonstrating rates <30% and others reaching up to >90% rates. One of the first studies to use neoadjuvant chemoradiation for patients radiographically classified as having BR disease was a phase II trial in which 18 BR and 10 unresectable PDAC patients underwent neoadjuvant 3-dimensional conformal RT (3D-CRT) to 45 Gy using 1.8 Gy/fraction combined with gemcitabine (31). Of the 18 patients, 7 (39%) ultimately underwent PD, with 6 patients

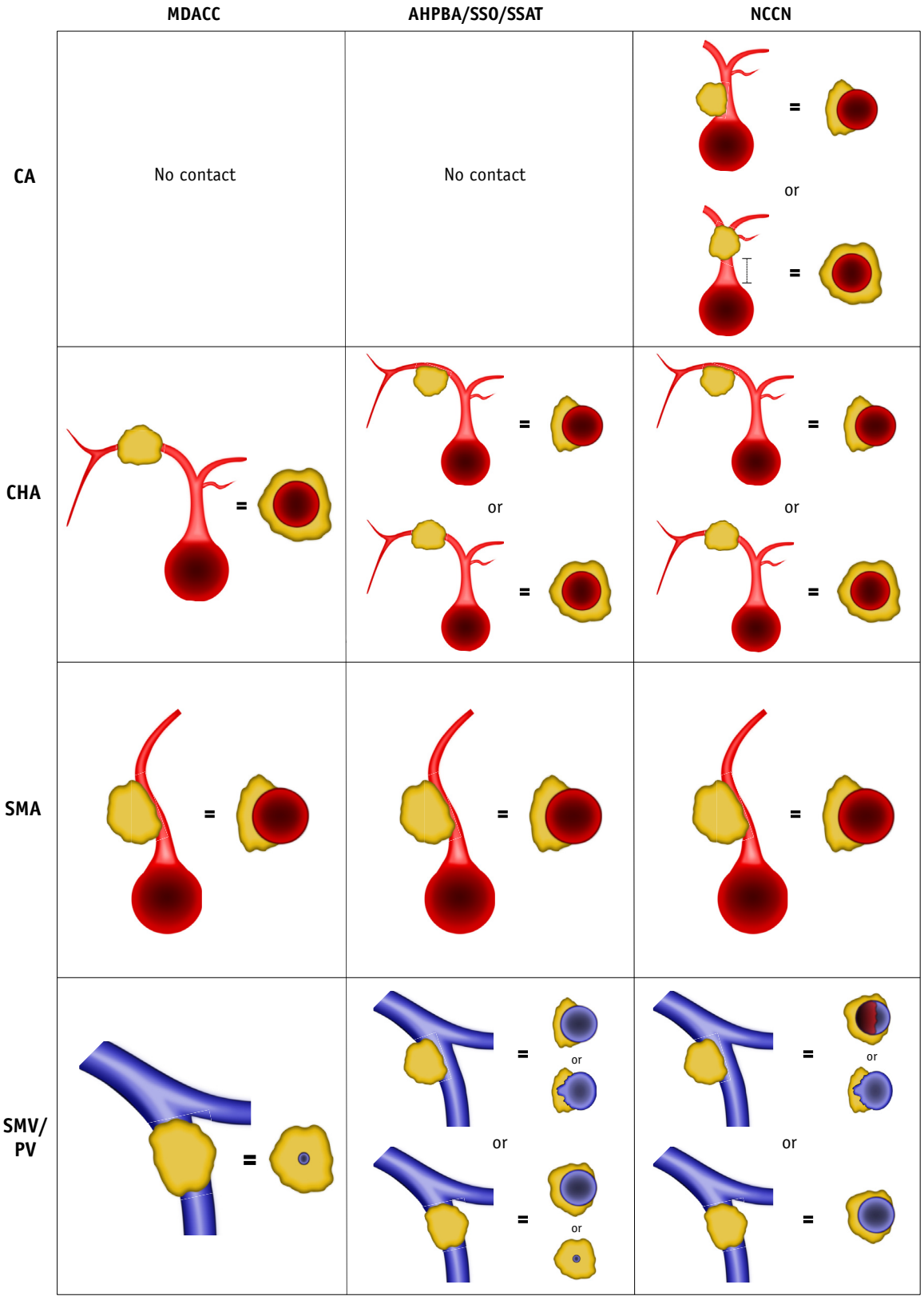

Fig. 3. Schematic representation of borderline resectable pancreatic cancer according to the MD Anderson Cancer Center (MDACC), Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT), and most recent version of National Comprehensive Cancer Network (NCCN) resectability criteria. Corresponds with data in Table 1. *Abbreviations:* CA = celiac axis; CHA = common hepatic artery; SMA = superior mesenteric artery; SMV = superior mesenteric vein; PV = portal vein.

(33.3%) achieving negative margins. The median OS for the BR group was 15.4 months.

Stokes et al (32) reported the outcomes of 40 BR patients defined using the MDACC criteria who underwent neoadjuvant chemoradiation. Patients received either 50.4 Gy in 28 fractions or 50 Gy in 20 fractions with concurrent capecitabine. Of the 34 patients who completed neoadjuvant therapy, 16 (40%) were amenable to PD and 14 (88%) achieved negative margins. The median OS for the whole group was 12 months; however, for the resected group, it was 23 months compared with only 3 months for the unresected group ($P = .0002$) (32).

In another study by Takai et al (33), 32 BR patients classified using the NCCN criteria were treated to 40 Gy in 2-Gy fractions with concurrent continuous infusion 5-fluorouracil (5-FU; 200 mg/m^2/d) and an intermittent cisplatin bolus (3-6 mg/m^2/d) for 4 weeks or weekly gemcitabine (400 mg/m^2) for 3 weeks. Patients then underwent restaging, and those without disease progression underwent PD with extended lymphadenectomy. The group that received gemcitabine-based chemoradiation demonstrated less disease progression compared with the group receiving 5-FU−based chemoradiation (5.6% vs 42.9%). Resection was possible for 24 patients (75%), with a median OS of 20.5 months but no significant difference between gemcitabine-based and 5-FU−based chemoradiation (26 vs 19.9 months) (33).

Cho et al (34) reported the outcomes from a series of 51 patients with BR disease who underwent resection. Of the 51 patients, 30 received neoadjuvant chemoradiation and 21 underwent upfront surgery. A total dose of 45, 50.4, or 58.4 Gy was applied at 1.8 Gy/fraction. Concurrent chemotherapy consisted mostly of gemcitabine alone, with cisplatin or capecitabine added to the gemcitabine at the physician's discretion. Although both groups achieved high rates of R0 resection (96.7% vs 95.2%), the group treated with neoadjuvant chemoradiation had a significantly lower recurrence rate (50% vs 81.6%; $P = .028$) and better median OS (45 vs 23.5 months; $P = .045$).

Habermehl et al (35) reported a retrospective analysis of 215 PDAC patients considered to have unresectable disease at diagnosis who underwent neoadjuvant 3D-CRT (median 52.2 Gy in 29 fractions) concurrently with gemcitabine (300 mg/m^2 weekly). After chemoradiation, the patients received full-dose gemcitabine (1000 mg/m^2 weekly) alone until disease progression or resection. After restaging, 104 patients (54%) underwent exploratory laparotomy; of these patients, 51 (26%) were able to undergo tumor resection, with negative margins in 39.2%. Intraoperative RT (IORT) was used in 26 patients, with a median dose of 15 Gy. The median OS was 22.1 months for R0, 15.6 months for R1, and 10.3 months for R2 resected patients.

The NEOPA (neoadjuvant treatment in resectable pancreatic cancer) trial (ClinicalTrials.gov identifier NCT01900327) is an ongoing multicenter phase III trial randomizing resectable and BR patients between neoadjuvant gemcitabine-based chemoradiation and upfront surgery, with both receiving adjuvant treatment with gemcitabine. The results from this trial will further define the role of neoadjuvant gemcitabine-based chemoradiation for BR patients. The outcomes from reported studies using neoadjuvant chemoradiation for BR patients are listed in Table 2.

Neoadjuvant chemotherapy alone

Several studies have reported the outcomes with neoadjuvant chemotherapy alone for BR patients, with results listed in Table 3. Sahora et al (44) reported a single-institution phase II trial using neoadjuvant gemcitabine and docetaxel for BR (n = 12) or unresectable (n = 13) disease. Two cycles were administered over 8 weeks. After restaging, 15 patients underwent surgical exploration and 8 ultimately underwent resection, of whom, 4 were BR patients. The median OS was 16.3 months (95% confidence interval [CI] 8.5-24.0) for resected patients and 12.2 months (95% CI 7.8-16.5) for unresected patients (P = NS). The same group reported another phase II trial testing the benefit of neoadjuvant gemcitabine and oxaliplatin on 25 patients with locally advanced disease, 15 considered BR. After 6 to 9 cycles of chemotherapy, 8 of 25 total patients (32%) and 7 of 15 BR patients (46%) underwent resection, 69% with negative margins (45).

Another phase II trial tested neoadjuvant gemcitabine and capecitabine for 43 patients with locally advanced disease, 18 of whom were considered to have BR disease using the NCCN criteria. Among these BR patients, 11 (61%) underwent resection, 9 (81.8%) with negative margins. Adjuvant chemotherapy was given to most R0 resected patients, and chemoradiation (60 Gy in 2-Gy fractions, with concurrent capecitabine) was given to unresected patients. Better OS was achieved in the patients who had undergone surgery compared with those who had not (23.1 vs 13.2 months; hazard ratio [HR] 0.43; 95% CI 0.21-0.88; $P = .017$) (46).

Based on the promising results reported by Conroy et al (55) with the use of FOLFIRINOX (5-FU, folinic acid, irinotecan, oxaliplatin) compared with gemcitabine for the treatment of metastatic disease, attempts have been made to obtain similar responses using FOLFIRINOX for borderline and unresectable patients. Paniccia et al (49) reported the outcomes of 20 BR patients treated with neoadjuvant FOLFIRINOX, followed by restaging. Two patients were lost to follow-up during chemotherapy and were excluded from the analysis. Ultimately, 17 of the 18 eligible patients (94%) underwent resection with negative margins. On pathologic examination, a complete tumor response was observed in 1 patient (5.9%), a partial response in 9 patients (52.9%), and a poor or no response in 7 patients (41.2%). With a median follow-up of 14.5 months, the median OS was not yet reached (49).

The superiority of gemcitabine plus nab-paclitaxel compared with gemcitabine alone for metastatic PDAC

Table 2 Major studies of neoadjuvant chemoradiation for borderline resectable pancreatic cancer

Investigator	Year	Study type	Patients (n)	BR* (n)	Criteria	Chemotherapy
Massucco et al (31)	2006	Phase II	28	18	Other	Sensitizer: gemcitabine
Brown et al (36)	2008	R	13	13	NCCN	Sensitizer: gemcitabine, 5-FU, capecitabine, or bevacizumab; ST: gemcitabine, gemcitabine + oxaliplatin, erlotinib, or bevacizumab
Takai et al (33)	2008	R	32	32	NCCN	Sensitizer: 5-FU + cisplatin or gemcitabine
Chun et al (37)	2010	R	109	74	Other	Sensitizer: gemcitabine or 5-FU
Stokes et al (32)	2011	R	40	34	MDACC	Sensitizer: capecitabine (chronomodulated)
Barugola et al (38)	2012	R	403	27	Other	Sensitizer: gemcitabine, cisplatin, or capecitabine; ST: gemcitabine ± oxaliplatin or capecitabine
Kang et al (39)	2012	R	136	32	NCCN	Sensitizer: gemcitabine ± cisplatin
Kim et al (40)	2013	Phase II	68	39	NCCN	Sensitizer: gemcitabine + oxaliplatin
Cho et al (34)	2013	R	51	30	MDACC	Sensitizer: gemcitabine ± cisplatin or capecitabine
Takahashi et al (41)	2013	R	268	80	MDACC	Sensitizer: gemcitabine
Hirono et al (42)	2016	R	377	46	NCCN	Sensitizer: S-1; ST: S-1 + gemcitabine

Abbreviations: 2D = 2-dimensional; 3D-CRT = 3-dimensional conformal radiation therapy; 5-FU = 5-fluorouracil; BR = borderline resectable; ChT = chemotherapy; Fx = fraction; MDACC = MD Anderson Cancer Center; NA = not applicable; NCCN = National Comprehensive Cancer Network; Not res = not resected; NR = not reported; NRd = not reached; OS = overall survival; R = retrospective; Res = resected; RT = radiation therapy; ST = systemic therapy.

* Patients with borderline resectable disease that received neoadjuvant therapy.

† By study design.

treated in the MPACT trial (56) set the basis for prospective studies testing neoadjuvant gemcitabine plus nab-paclitaxel in BR and locally advanced patients with promising outcomes. Ielpo et al (51) observed a 68% resection rate after neoadjuvant gemcitabine plus nab-paclitaxel among 25 potentially resectable PDAC patients, of whom 11 had BR disease, with 8 (72%) undergoing successful R0 resection. Adjuvant gemcitabine was administered to all patients. The median OS was 21 months for those who underwent resection (51). Ongoing phase II and III trials are testing the efficacy of this regimen in BR patients against other therapies.

Induction chemotherapy followed by neoadjuvant chemoradiation

Many studies have combined induction chemotherapy with chemoradiation to address the potential for microscopic metastatic disease and still allow for intensified locoregional treatment to sterilize the tumor boundaries in contact with the abutted or encased vessel (Table 4).

Katz et al (57) reported on a large series from the MD Anderson Cancer Center (Houston, TX), including 160 BR cases. Among them, 84 patients were considered to have BR by anatomic criteria (group A), 44 patients had suspected metastatic disease (group B), and 32 patients had poor performance status precluding immediate resection (group C). Most patients were preoperatively treated with induction gemcitabine-based chemotherapy for 2 to 4 months followed by chemoradiation (50.4 Gy in 28 fractions or 30 Gy in 10 fractions with concomitant 5-FU, paclitaxel, gemcitabine, or capecitabine). For group A, 32 (38%) eventually underwent resection, all but 1 patient (96.8%) with negative margins. The median OS for group A was 40 months for the resected group versus 15 months for the unresected group ($P = .001$).

In the LAP07 trial, stage III PDAC patients were randomized initially between gemcitabine plus erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, versus gemcitabine alone for 4 cycles. Those without progression were then randomized between chemoradiation (3D-CRT to 54 Gy in 30 daily fractions with concurrent capecitabine) versus gemcitabine for an additional 2 months. No benefit for progression-free survival (PFS) or OS was observed with the addition of erlotinib in the first randomization, and no survival advantage was observed with chemoradiation in the second randomization, despite improved PFS. Although stage III (T4 anyN M0) encompasses patients with any degree (>0°) of tumor contact with the SMA or CA, based on the number of patients who underwent resection after the first randomization treatment (n = 6) and the second randomization treatment (n = 12), 4% overall, we estimated that most patients in that study had locally advanced/unresectable tumors (>180° of arterial involvement) and a very small number of BR cases. The LAP07 findings must be taken with caution when applying it to BR PDAC (68).

Investigators from the Medical College of Wisconsin reported the results of 18 BR patients treated with induction FOLFIRINOX, followed by chemoradiation, consisting of 50.4 Gy in 28 daily fractions combined with gemcitabine or capecitabine. Fifteen of 18 patients (83%) underwent attempted surgery, with 3 (20%) found to have occult metastatic disease intraoperatively; 12 (80%) successfully underwent R0 resection. Eleven tumor specimens had a >50% pathologic response. At a median of 22 months after

Table 2 Major studies of neoadjuvant chemoradiation for borderline resectable pancreatic cancer *(continued)*

RT dose (Gy)	Dose/Fx	RT technique	BR resected (%)	Negative margins*	Median OS of BR (mo)		
					All	Res	Not res
45	1.8	3D-CRT	39	87.5	15.4	>21	10
50.4	1.8	NR	100†	84.6	NRd	NRd	NA
40	2	3D-CRT	75	NR	19.2	20.5	5.5
NR	NR	NR	100†	59	23	23	NA
50.4/50	1.8/2.5	3D-CRT or tomotherapy	40	88	12	23	3
50.4/45	1.8	NR	100†	70.7	35	35	NA
50.4/45	1.8	2D- or 3D-CRT	100†	84.3	26.3	26.3	NA
30	2	3D-CRT	71.8	NR	18.4	25.4	NR
45/50.4/58.4	1.8	3D-CRT or tomotherapy	100†	96.7	45	45	NA
50	2	3D-CRT	54	98	NR	NR	14
50	2	3D-CRT	86.9	NR	12.4	14.4	8.6

the diagnosis, 7 of the 12 resected patients (58.3%) were still alive and all unresected patients had died. The median OS was 12.5 months (64).

The ALLIANCE (Alliance for Clinical Trials in Oncology) A021101 was a prospective single-arm trial that evaluated FOLFIRINOX for 4 cycles, followed by chemoradiation (50.4 Gy in 28 daily fractions) with capecitabine, in 22 BR patients using the Intergroup resectability criteria (19, 67). Four patients developed progression during FOLFIRINOX (n = 1) or chemoradiation (n = 3), and 2 patients had suspected metastases and surgery was aborted. Ultimately, 15 patients (68.2%) underwent PD, 14 (93%) of whom had negative margins. Patients who underwent PD had an 18-month OS rate of 67% versus 43% for those who had not undergone PD (HR 0.13; 95% CI 0.03-0.48; $P = .001$). The median survival for the overall group was 21.7 months.

Neoadjuvant chemoradiation intensification

Incorporation of RT into neoadjuvant therapy has been shown to increase resectability rates and improve the histologic treatment response of BR PDAC (32). With the intent of increasing efficacy, different fractionation schedules and/or increasing radiation doses have been tested in combination with chemotherapy.

Chakraborty et al (69) reported the results of a hypofractionated RT study using intensity modulated RT (IMRT) in which 13 BR patients were treated with 50 Gy in 20 fractions of 2.5 Gy/fraction, concurrently with capecitabine 825 mg/m^2 twice daily. That study was stopped before the planned interim analysis because of 2 severe (1 grade 4 and 1 grade 5) gastric ulcerations. Only 5 patients were able to undergo resection, 4 of whom had negative margins. The median OS for the resected patients was not reached.

Using a lower total dose, Takeda et al (70) reported the outcomes of an accelerated hyperfractioned RT approach with concurrent gemcitabine in a phase I/II trial. Of the 35 BR patients, 32 were treated with 36 Gy and 3 with 30 Gy, delivered in 1.5-Gy fractions twice daily using 4-field box technique. In the phase I portion, increasing dose levels of gemcitabine were tested, ultimately reaching 800 mg/m^2 once a week, which was used for the phase II portion (n = 26). The toxicity rates were low, and, ultimately, 26 patients (74.3%) underwent resection, 75% of whom had R0 resection margins. The median OS was 41.2 months, and 5 patients were alive with >5 years of follow-up.

Improved response and resectability have been attempted through radiation dose escalation to areas of the tumor−vessel interface. A radiation dose boost is usually delivered through IMRT, which allows for greater target conformality and avoidance of an increase in gastrointestinal toxicity rates (71). In a retrospective report of 103 BR patients treated with neoadjuvant chemoradiation, 23 received a RT boost to a median dose of 54 Gy (range 54-64) to the tumor−vessel interface, and 80 received a standard dose of 50.4 Gy. A trend toward increased resection rates and OS was observed, favoring the group that received the higher dose (odds ratio 2.77; 95% CI 0.89-8.57; $P = .077$) (72). The use of hypofractionated IMRT with a simultaneous integrated boost (SIB) to the involved vessels was tested after induction chemotherapy for stage III/IV PDAC by an Italian group (73). In that phase I trial, 44.25 Gy in 15 fractions with concurrent capecitabine was delivered to the whole tumor, with escalating doses delivered using a SIB to a 1-cm expansion around

Table 3 Major studies of neoadjuvant chemotherapy for borderline resectable pancreatic cancer

Investigator	Year	Study type	Patients (n)	BR* (n)	Criteria	Chemotherapy
McClaine et al (43)	2009	R	29	29	MDACC/NCCN	Gemcitabine ± erlotinib ± oxaliplatin; 9 patients received chemo-RT
Sahora et al (44)	2011	Phase II	25	12	AHPBA/SSO/SSAT	Gemcitabine + docetaxel
Sahora et al (45)	2011	Phase II	33	15	AHPBA/SSO/SSAT	Gemcitabine + oxaliplatin
Lee et al (46)	2012	Phase II	43	18	NCCN	Gemcitabine + capecitabine
Boone et al (47)	2013	R	25	12	AHPBA/SSO/SSAT	FOLFIRINOX; 4 patients received chemo-RT
Motoi et al (48)	2013	Phase II	36	16	NCCN	Gemcitabine + S-1
Paniccia et al (49)	2014	R	20	20	NCCN	FOLFIRINOX; 8 patients received chemo-RT
Rose et al (50)	2014	R	64	64	AHPBA/SSO/SSAT	Gemcitabine + docetaxel; 2 patients received chemo-RT
Ielpo et al (51)	2016	Phase II	25	11	NCCN	Gemcitabine + nab-paclitaxel
Kim et al (52)	2016	R	26	14	NCCN	FOLFIRINOX; 4 patients received chemo-RT
Murakami et al (53)	2016	R	77	52	NCCN	Gemcitabine + S-1
Okada et al (54)	2017	Phase I	10	10	NCCN	Gemcitabine + nab-paclitaxel

Abbreviations: AHPBA/SSO/SSAT = Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; BR = borderline resectable; chemo-RT = chemoradiation; FOLFIRINOX = 5-fluorouracil, folinic acid, irinotecan, oxaliplatin; MDACC = MD Anderson Cancer Center; Not res = not resected; NCCN = National Comprehensive Cancer Network; NR = not reported; NRd = not reached; OS = overall survival; R = retrospective; Res = resected; RT = radiation therapy.

* Patients with borderline resectable disease who underwent neoadjuvant therapy.

† By study design.

the infiltrated vessel plus the PTV margins. One patient who received 50 Gy developed an acute dose-limiting toxicity (grade 3 gastric ulcer). Three patients developed grade 3 late toxicities associated with gastric and/or duodenal mucosal injury. After treatment, 5 of 24 evaluable patients (21%) experienced a radiologic partial response, 16 (67%) had stable disease, and 3 (12.5%) had progressive disease; however, ultimately, only 1 patient underwent R0 resection. The median PFS and OS were 12.1 and 19.7 months, respectively.

A retrospective analysis from MDACC reported the outcomes of locally advanced patients receiving chemoradiation who received focal dose escalation (biologically effective dose [BED] >70 Gy, mostly using IMRT) compared with standard doses of BED ≤70 Gy. The boost was delivered to areas of greater risk of recurrence or gross tumor away from the gastrointestinal mucosa. All patients underwent irradiation after induction FOLFIRINOX or gemcitabine-based chemotherapy. Patients who received BED >70 Gy (n = 47) had a superior median OS (17.8 vs 15.0 months; $P = .03$) compared with those treated with lower doses, with an estimated OS rate of 31% versus 9% at 3 years. Similarly, locoregional control was superior for patients who received higher RT doses (74).

More recently, the RTOG (Radiation Therapy Oncology Group) 1201 study, a multicenter randomized phase II trial, tested whether an intensified chemoradiation regimen (63 Gy in 28 fractions through IMRT) after induction gemcitabine plus nab-paclitaxel would improve OS for patients with unresectable pancreatic cancer (ClinicalTrials.gov identifier NCT01921751). In addition, the study tried to address the role of gene *SMAD4* expression on patterns of disease progression. However, the trial was terminated early because of slow accrual.

Induction chemotherapy and neoadjuvant stereotactic body RT

Since the report of the first prospective trial of stereotactic body RT (SBRT) for locally advanced PDAC by Koong et al (75) in 2004, many other studies have confirmed the excellent local control rates achieved with this modality (76-80). Moreover, the possibility of combining ablative radiation doses to the tumor and minimizing interruption of systemic therapy has made SBRT an attractive option for the treatment of BR disease (Table 5).

Herman et al (80) reported the results of the first multiinstitutional phase II trial of chemotherapy followed by SBRT for unresectable PDAC. Patients received ≤3 weeks of gemcitabine, followed by 33 Gy delivered in 5 consecutive daily fractions. After SBRT, the patients continued treatment with gemcitabine until disease progression or limiting toxicity. Of the 49 patients available for analysis, 5 (10%) were deemed to have resectable disease. Four patients (8%) underwent successful margin-negative resection, and one refused surgery. The median OS was 13.9 months, and the freedom from local disease progression at 1 year was 78%.

Chuong et al (81) reported a series of 73 patients with PDAC, 57 with BR disease, who underwent SBRT after induction chemotherapy. Gemcitabine combined with docetaxel and oxaliplatin was the most common induction regimen. SBRT was delivered in 5 consecutive daily fractions to a median dose of 30 Gy, with an SIB to the tumor–vessel interface up to 50 Gy (median 35 Gy). Afterward, 32 of the 57 borderline patients (56%) underwent resection, 31 (97%) with negative margins and 3 (9.3%) with a complete pathologic response. The median OS was

Table 3 Major studies of neoadjuvant chemotherapy for borderline resectable pancreatic cancer *(continued)*

Therapy duration	BR resected (%)	Negative margins* (%)	Median OS of BR* (mo)		
			All	Res	Not res
Res: 104 ± 37 d; not res: 121 ± 73 d	41.4	67	NR	23.3	15.5
2 cycles in 8 wk	33.3	NR	NR	NR	NR
6 wk ± 3 wk	46.7	NR	NR	NR	NR
3 Cycles ± 3 cycles	61	81.8	NR	NR	NR
6 Cycles	58.3	55	NR	NR	NR
2 Cycles	NR	NR	NR	NR	NR
4 Cycles	85	100	NRd	NRd	NR
8 Cycles	48.4	87	23.6	NRd	15.4
≥2 Cycles	72.7	100	20	NR	NR
9 Cycles	100†	92.3	NRd	NRd	NR
3 Cycles	90.3	72.3	27.1	27.2	13.3
2 Cycles	80	87.5	NR	NR	NR

19.3 months for the resected patients versus 12.3 months for the unresected patients ($P = .028$). An updated series from the same institution reported on the outcomes of 101 BR cases treated with a similar regimen of induction chemotherapy and SBRT, including SIB to the tumor−vessel interface. Fifty-five patients (54.5%) underwent resection, with 96.4% having negative margins. The median disease-specific survival for the resected patients was 43 months (85).

Increased pathologic response rates after induction chemotherapy and SBRT has been correlated with improved survival in BR PDAC. Chuong et al (87) reported superior OS and PFS for BR patients who underwent resection and achieved ≥10% of tumor destruction (grade IIa-IV using the MDACC criteria) after induction gemcitabine, docetaxel, and capecitabine, followed by SBRT, compared with those with <10% of tumor destruction. Excellent pathologic response rates were reported for 12 PDAC patients who underwent resection after induction chemotherapy and SBRT at the University of Pittsburgh Cancer Institute (82). With a median dose of 36 Gy in 3 fractions, 25% of patients achieved a complete pathologic response and 58.3% had ≥50% of tumor cell destruction.

Two important ongoing randomized multi-institutional clinical trials will help to define the role of neoadjuvant induction chemotherapy followed by SBRT for pancreatic cancer not resectable at presentation. The first is a phase III trial led by Stanford University in which patients with unresectable PDAC without disease progression after ≤4 cycles of modified FOLFIRINOX (mFOLFIRINOX) will be randomized between SBRT (40 Gy in 5 fractions) followed by mFOLFIRINOX versus mFOLFIRINOX alone until disease progression (ClinicalTrials.gov identifier NCT01926197). The second is the ALLIANCE A021501, a phase II trial randomizing BR PDAC of the head of the pancreas between neoadjuvant mFOLFIRINOX followed by PD and adjuvant FOLFOX (folinic acid, 5-FU, oxaliplatin), versus mFOLFIRINOX followed by SBRT and then PD and adjuvant FOLFOX (ClinicalTrials.gov identifier NCT02839343).

Neoadjuvant particle therapy

With the physical characteristics of the Bragg peak, particle therapy might have a role in treating PDAC owing to its ability to deposit the dose more conformally than photon therapy. Some clinical reports have suggested favorable disease outcomes.

Hong et al (88) reported the outcomes of a phase I/II trial of neoadjuvant proton-based chemoradiation for resectable PDAC using a dose of 25 Gy relative biological effectiveness in 5 fractions given concurrently with capecitabine 825 mg/m^2 twice daily for 2 weeks. The clinical target volume was defined as the gross tumor volume with a 1-cm margin, respecting the adjacent normal organs. Elective nodal basins included the celiac, porta hepatis, superior mesenteric artery and vein, and para-aortic. A total of 35 patients received the total dose, 2 of whom experienced grade 3 toxicity. However, no case of grade 4 or 5 toxicity developed. Of the 48 eligible patients, 37 underwent resection, 84% with negative margins, with a median OS of 27 months for the resected patients.

Table 4 Major studies of neoadjuvant induction chemotherapy followed by chemoradiation for borderline resectable pancreatic cancer

Investigator	Year	Study type	Patients (n)	BR* (n)	Criteria	Chemotherapy
Katz et al (57)	2008	R	160	84†	MDACC	Induction: gemcitabine; sensitizer: 5-FU, paclitaxel, gemcitabine, or capecitabine
Landry et al (58)	2010	Phase II, randomized	Arm A: 10; arm B: 11	A: 10; B: 11	Other	Arm A: sensitizer, gemcitabine; arm B: induction, gemcitabine + cisplatin + 5-FU, followed by sensitizer, 5-FU
Chuong et al (59)	2011	R	14	14	Other	Induction: gemcitabine + docetaxel + capecitabine; sensitizer: 5-FU
Patel et al (60)	2011	R	17	17	Other	Induction: gemcitabine + docetaxel + capecitabine; sensitizer: 5-FU
Kharofa et al (61)	2012	R	12	12	MCW	Induction: FOLFIRINOX; sensitizer: gemcitabine or capecitabine
Leone et al (62)	2013	R	39	15	AHPBA/ SSO/SSAT	Induction: gemcitabine + oxaliplatin; sensitizer: gemcitabine
Dholakia et al (63)	2013	R	50	50	AHPBA/ SSO/SSAT	Induction: FOLFIRINOX or 5-FU + oxaliplatin; sensitizer: gemcitabine ± oxaliplatin or capecitabine
Christians et al (64)	2014	R	18	18	MCW	Induction: FOLFIRINOX; sensitizer: gemcitabine or capecitabine
Kharofa et al (65)	2014	R	69	39	MCW	Induction: gemcitabine ± cisplatin or erlotinib; or FOLFIRINOX; sensitizer: gemcitabine or capecitabine
Badiyan et al (66)	2016	R	32	7	AHPBA/ SSO/SSAT	Induction: FOLFIRINOX or gemcitabine; sensitizer: gemcitabine
Katz et al (67)	2016	Prospective multicenter	22	22	Intergroup	Induction: modified FOLFIRINOX; sensitizer: capecitabine

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; 5-FU = 5-fluorouracil; Fx = fraction; AHPBA/SSO/SSAT = Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; BR = borderline resectable; IMRT = intensity modulated radiation therapy; MCW = Medical College of Wisconsin; MDACC = MD Anderson Cancer Center; NCCN = National Comprehensive Cancer Network; Not res = not resected; NR = not reported; NRd = not reached; OS = overall survival; R = retrospective; Res = resected; RT = radiation therapy; ST = systemic therapy; VMAT = volumetric modulated arc therapy.

* Patients with borderline resectable disease who underwent neoadjuvant therapy.

† Anatomically defined borderline resectable (type A according to Katz et al [57]).

‡ By study design.

The University of Florida treated PDAC and ampullary cancers patients neoadjuvantly using doses ≤59.4 Gy (relative biological effectiveness) in 33 fractions, combined with capecitabine, with a similarly low incidence of gastrointestinal toxicity (89). In a separate phase II trial, the same investigators treated 11 unresectable PDAC patients (90). They reported a median OS of 18.4 months, with 1- and 2-year OS rates of 61% and 31%, respectively. No patient experienced grade ≥2 gastrointestinal toxicity (90).

A phase I dose escalation trial of neoadjuvant hypofractionated carbon ion therapy for resectable PDAC was reported by investigators from the National Institute of Radiological Sciences (Chiba, Japan). In that study, 26 patients received a maximum dose of 36.8 GyE in 8 fractions, 21 (81%) of whom ultimately underwent surgery and 19 (90%) had negative margins. No local failure was observed. With a median follow-up of 33 months, the OS rates at 1, 3, and 5 years were 81%, 52%, and 52% for the resected patients, respectively (91). The same group reported on dose-escalation study using carbon ion therapy combined with concurrent gemcitabine that included 72 locally advanced PDAC patients. Doses started at 43.2 GyE and were escalated up to 55.2 GyE. Gastrointestinal grade 2 toxicities were observed in 7 patients (10%); 1 patient (1%) developed a late grade 3 bleeding gastric ulcer. The median OS was 19.6 months. Local pancreatic cancer progression or recurrence was observed in 17% patients using computed tomography (Response Evaluation Criteria In Solid Tumors [RECIST]); in contrast, using fludeoxyglucose positron emission tomography, it was 54% (92).

Targeted therapy and immunotherapy

Despite the advances obtained with cytotoxic combinations such as FOLFIRINOX and gemcitabine/nab-paclitaxel, the outcomes have remained unsatisfactory. Pancreatic cancer has a wide spectrum of genetic mutations, offering many possibilities for targeted therapy. Point mutations in K-ras and inactivation of tumor suppressor genes such as cyclin-dependent kinase inhibitor 2A (*CDKN2A*), tumor protein

Table 4 Major studies of neoadjuvant induction chemotherapy followed by chemoradiation for borderline resectable pancreatic cancer *(continued)*

RT dose (Gy)	Dose/Fx	RT technique	BR resected (%)	Negative margins (%)	Median OS of BR (mo)		
					All	Res	Not res
50.4/30	1.8/3	3D-CRT	38[†]	96.8[†]	21[†]	40[†]	15[†]
50.4	1.8	3D-CRT	23.8	40	A: 19.4; B: 13.4	26.3	NR
50	2	3D-CRT or IMRT	100[‡]	86	NR	NR	NR
50	2	IMRT	47	88.9	15.6	NRd	NR
50.4	1.8	IMRT	58	100	NRd	NRd	NR
50.4	1.8	3D-CRT	60	NR	27.8	32	NR
50/30	2/3	3D-CRT, IMRT or VMAT	58	93	17.2	22.9	13
50.4	1.8	IMRT	80	NR	NR	NRd	12.5
50.4	1.8	IMRT	56.4	100	NR	NR	NR
55	2.2	IMRT	57.1	90	NR	NR	NR
50.4	1.8	3D-CRT or IMRT	68.2	93	21.7	NR	NR

p53 (*TP53*), and *SMAD4* are all commonly identified mutations in pancreatic cancer (93).

Crane et al tested the efficacy of adding cetuximab, an epidermal growth factor receptor inhibitor, to gemcitabine plus oxaliplatin, followed by chemoradiation, in a phase II trial of 69 locally advanced PDAC patients, including 16 BR patients. Nine patients with BR disease (56.2%) underwent resection, all with negative margins. The median OS for the whole group was 19.2 months. The patients who maintained *SMAD4* expression showed a local dominant pattern of disease progression (94). Esnaola et al (95) also tested the effect of combining cetuximab with gemcitabine and oxaliplatin but with selective use of neoadjuvant chemoradiation in a phase II trial of 13 borderline and 24 unresectable patients. On restaging, the patients who were considered resectable, showing no tumor abutment/encasement of the adjacent celiac axis, common hepatic artery, SMA, and/or the SMV/PV confluence, underwent surgery. Patients with stable disease received chemoradiation, and patients with evidence of disease progression were removed from the protocol. Overall, 11 patients (29.7%) underwent successful R0 surgical resection, including 9 of the 13 patients with borderline disease (69.2%).

Although the initial clinical experience with pancreatic cancer was promising, randomized data could not demonstrate a significant benefit for erlotinib compared with chemotherapy alone. The combination of gemcitabine with erlotinib was evaluated in a phase III trial of 569 locally advanced (n = 138) or metastatic (n = 431) pancreatic cancer patients. On the intention-to-treat analysis, the group receiving gemcitabine plus erlotinib demonstrated only a very small improvement in median OS compared with the gemcitabine plus placebo group (6.24 vs 5.91 months; HR 0.82; 95% CI 0.69-0.99; $P = .038$) (96). However, no benefit in PFS or OS was observed for locally advanced patients in the LAP07 trial between gemcitabine plus erlotinib versus gemcitabine alone for locally advanced PDAC (68). Erlotinib was also not beneficial when added to gemcitabine in the adjuvant setting for R0 resected patients in the randomized phase III CONKO-005 trial (97).

Neoadjuvant fixed-dose rate gemcitabine combined with the vascular endothelial growth factor A inhibitor

Table 5 Major studies of neoadjuvant chemotherapy and stereotactic body radiation therapy for borderline resectable pancreatic cancer

Investigator	Year	Study type	Patients (n)	BR* (n)	Criteria	Chemotherapy
Chuong et al (81)	2013	R	73	57	NCCN	Induction: mostly gemcitabine + docetaxel + oxaliplatin
Rajagopalan et al (82)	2013	R	12	7	MDACC	Induction: mostly gemcitabine + capecitabine
Mellon et al (83)	2015	R	169	110	NCCN	Induction: mostly gemcitabine + docetaxel + oxaliplatin
Moningi et al (84)	2015	R	88	14	AHPBA/ SSO/SSAT	Induction: gemcitabine ± cisplatin, 5-FU, or nab-paclitaxel; or FOLFIRINOX
Rashid et al (85)	2016	R	101	101	NCCN	Induction: gemcitabine + docetaxel + oxaliplatin
Shaib et al (86)	2016	Phase I	13	13	Intergroup	Induction: mFOLFIRINOX

Abbreviations: 5-FU = 5-fluorouracil; AHPBA/SSO/SSAT = Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; BR = borderline resectable; FOLFIRINOX = 5-fluorouracil, folinic acid, irinotecan, oxaliplatin; Fx = fraction; OS = overall survival; MDACC = MD Anderson Cancer Center; mFOLFIRINOX = modified 5-fluorouracil, folinic acid, irinotecan, oxaliplatin; NA = not applicable; NCCN = National Comprehensive Cancer Network; Not res = not resected; NR = not reported; NRd = not reached; Res = resected; RT = radiation therapy.

Data in brackets are doses delivered by a simultaneous integrated boost.

* Patients with borderline resectable disease who underwent neoadjuvant therapy.

† By study design.

bevacizumab and accelerated RT (30 Gy in 10 fractions) was tested in potentially resectable PDAC patients in a phase II trial. Of the 59 patients enrolled, 43 (73%) underwent resection (4 developed radiographic progression and 10 carcinomatosis on diagnostic laparoscopy). Of the 43 patients who underwent resection, 38 (88%) had negative margins. The median OS was 16.8 months for the entire cohort and was 19.7 for the resected group. Nineteen cases (32.8%) of grade 3 toxicity occurred (98). Bevacizumab was combined with gemcitabine without radiation in another phase II trial, including 11 borderline and 19 unresectable PDAC patients (99). Six of the 11 BR patients (55%) underwent resection; however, the median OS was only 13 months, because 3 patients died of postoperative complications.

In a nonrandomized, phase 1B study conducted by Washington University, a CCR2 inhibitor was combined with FOLFIRINOX in BR or locally advanced PDAC patients. A total of 47 patients were treated, without dose-limiting toxicity. Of the 33 patients receiving FOLFIRINOX plus the CCR2 inhibitor, 16 (49%) demonstrated an objective tumor response, with local control achieved in 32 patients (97%). In the FOLFIRINOX-alone group, none of the 5 patients achieved an objective tumor response (100).

Other targeted agents have been tested in phase II/III trials in the metastatic or locally advanced disease setting, such as trastuzumab (targeting HER2), marimastat (targeting matrix metalloproteinase), vismodegib (targeting Hedgehog), olaparib (targeting poly [ADP-ribose] polymerase), ganitumab (targeting insulin-like growth factor 1 receptor), and tipifarnib (targeting Ras), but without a demonstrable impact on the survival rates (101).

More recently, immune checkpoint inhibitors such as anti-programmed cell death protein 1 (PD-1), PD ligand 1 (PD-L1), or cytotoxic T-lymphocyte antigen 4 have all demonstrated efficacy and impressive tumor response rates in many cancer types, with some metastatic cases showing complete responses (102). Furthermore, studies that have included advanced PDAC patients showing mismatch repair deficiency (or microsatellite instability) have shown significant disease control rates (70%-90%) when given PD-1 inhibitors (103, 104). The rate of mismatch repair deficiency in PDAC was shown to only be 1%.

It has been demonstrated in vivo that immune checkpoint inhibitors such as anti−PD-L1 might enhance the radiation response in PDAC. Using murine pancreatic cancer allografts, the blockade of PD-L1 improved the tumor response to high radiation doses and reduced the development of liver metastasis (105). These data await clinical confirmation (106), and further investigation is ongoing.

Response assessment after neoadjuvant therapy

Restaging of BR pancreatic cancer after neoadjuvant chemotherapy and RT is an additional challenge. Although the ultimate goal of neoadjuvant therapy is "downstaging" of the disease, radiographic changes are often not apparent or can be obscured by post-treatment inflammatory changes (63, 107) owing to the desmoplastic nature of these tumors (108).

In a retrospective study of 47 resected PDAC patients after induction FOLFIRINOX with or without sequential chemoradiation, a senior pancreatic surgeon, who was unaware of the timing of the scans, deemed most patients as still borderline or unresectable after therapy (109). However, all the patients had undergone resection with a 92% R0 rate (109).

Table 5 Major studies of neoadjuvant chemotherapy and stereotactic body radiation therapy for borderline resectable pancreatic cancer *(continued)*

				Median OS of BR (mo)		
RT dose (Gy)	Dose/Fx	BR resected (%)	Negative margins*	All	Res	Not res
30 [35]	6 [7]	56.1	96.8	16.4	NR	NR
36	12	100†	91.7	47.2	47.2	NA
30 [40]	6 [8]	51	96	19.2	NR	NR
33	6.6	28.5	NR	14.4	NR	NR
30 [40]	6 [8]	54.5	96.4	18	33	14
36 [45]	12 [15]	66.7	100	11	NRd	NR

Similarly, Katz et al (110) reported a retrospective analysis of 129 BR patients, of whom, 122 underwent restaging after neoadjuvant therapy. Using the RECIST, 84 patients (69%) had stable disease, 15 patients (12%) had a partial response, and 23 patients (19%) had progressive disease, with only 1 patient (0.8%) downstaged to resectable status using the MDACC resectability criteria. Despite these findings, 85 patients (66%) underwent pancreatectomy, with a 95% rate of negative margins. Based on these results, they appropriately recommended that in the absence of metastatic disease or limiting performance, surgical resection should still be attempted for BR cases after neoadjuvant therapy (110). From a cohort of 81 PDAC patients who underwent resection after neoadjuvant chemotherapy and SBRT, 73 with BR disease, Mellon et al (111) did not observe a correlation of preoperative restaging using computed tomography (RECIST) with the final tumor regression grade on pathologic examination.

Metabolic tumor activity has been also investigated for predicting the response after neoadjuvant therapy (112). From a cohort of 83 patients with resectable or BR disease presenting with a fludeoxyglucose-avid tumor before receiving neoadjuvant chemoradiation, followed by radical surgery, Akita et al (113) demonstrated that the maximal standardized uptake value (SUVmax) after chemoradiation was significantly lower in good responders using the Evans grade compared with poor responders, with an ideal threshold of 50% reduction in the SUVmax for detecting a good response. Moreover, the 5-year OS rate for patients with a high SUVmax regression index ($\geq$50%) was 56.0%, significantly greater than the 36.6% for patients with a low regression index (<50%; $P = .031$) (113).

Surgical technique

Given that the ultimate goal for BR pancreatic cancer is complete resection with microscopically negative margins, more aggressive surgical procedures might be required, including PV/SMV resection and, more rarely, resection of major arteries during PD. Although these techniques have been explored since the 1950s, with controversial results (114), more recent developments in radiographic imaging, surgical technique, and perioperative care have allowed for the resurgence of more aggressive pancreatic surgery, offering patients previously deemed to have borderline or unresectable disease, the possibility of undergoing curative resection (115-117). A meta-analysis reported in 2012 of 2908 patients with resected PDAC, 661 of whom had portomesenteric venous resections, demonstrated no difference in OS compared with patients without venous resection (118).

Arterial resection is still considered controversial and should be attempted only at tertiary centers by surgeons with expertise in the management of pancreatic cancer. A recent meta-analysis demonstrated that arterial reconstruction was associated with a fivefold increase in perioperative mortality and a 50% decrease in 1-year survival compared with patients undergoing pancreatectomy without any vascular reconstruction (119). However, the 3 specific arteries (celiac, SMA, and common hepatic) that might be involved with these BR tumors should be considered individually, because each carries its own risk profile. Tumors with celiac axis encasement can have the celiac axis resected if en bloc resection of the stomach and pancreatic tail is also undertaken. This procedure was first described by Appleby in 1953, for whom the

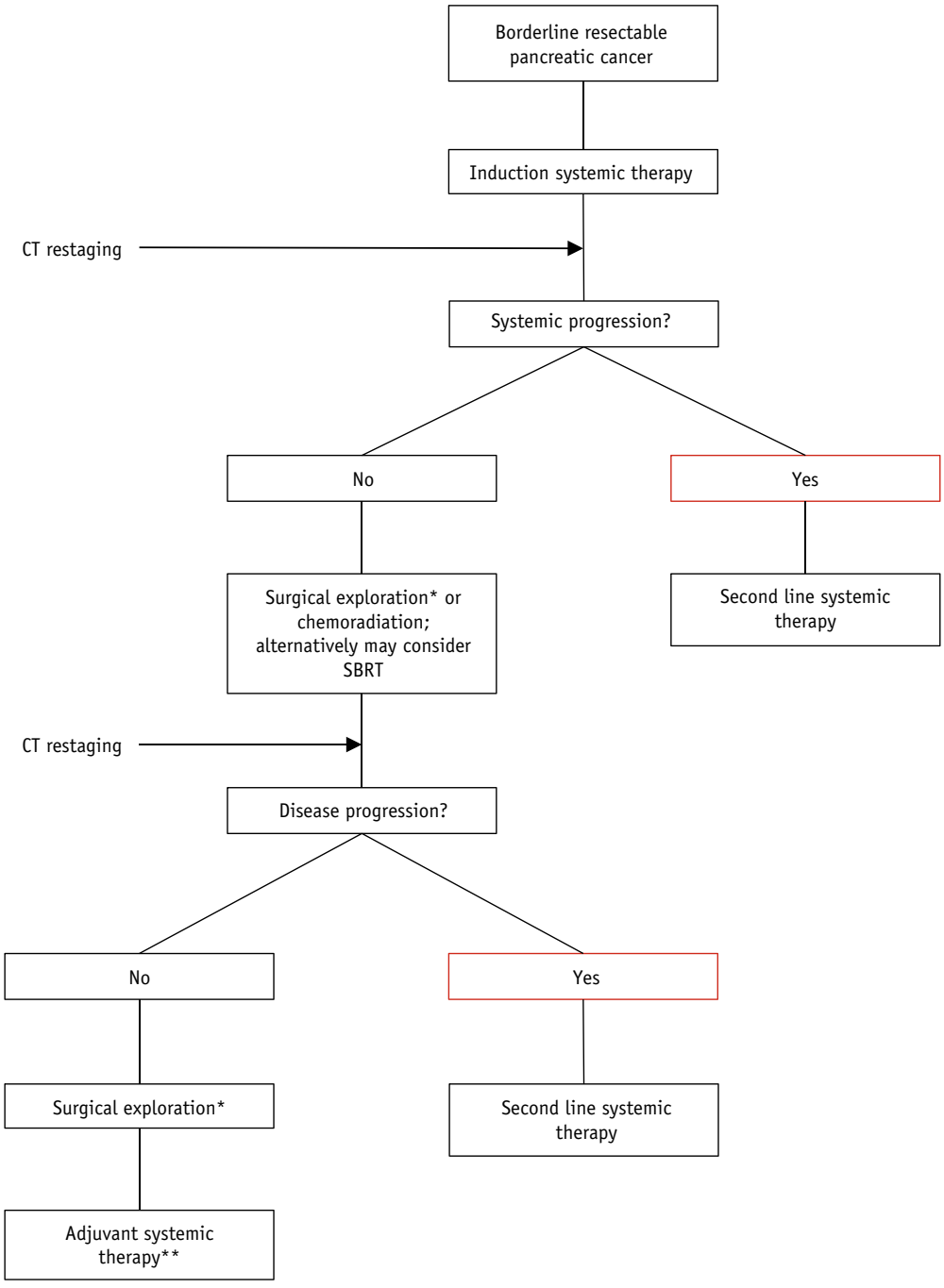

Fig. 4. Suggested treatment algorithm for borderline resectable pancreatic adenocarcinoma. *In the absence of local disease progression that precludes surgical resection. Preferably performed by surgeons with expertise in pancreatic cancer management. **Consider the use of intraoperative radiation therapy in the case of positive margins or a high risk of positive margins. *Abbreviations:* CT = computed tomography; SBRT = stereotactic body radiation therapy; TB = total bilirubin.

procedure is named. Currently, modified versions of the Appleby procedure are used for tumors of the body and tail of the pancreas involving the celiac axis but are reserved for selected cases at experienced institutions, with some series demonstrating rates of morbidity similar to those with conventional PD (120, 121). Investigators from Columbia University reported on 61 locally advanced PDAC patients who underwent tumor resection despite showing >180° of arterial encasement on restaging computed tomography after neoadjuvant chemotherapy, followed by SBRT or IMRT. A Whipple procedure was performed in 60.6%, an Appleby in 18%, and distal pancreatectomy in 21.5% of the patients. Most patients also underwent irreversible electroporation. Ultimately, R0 resection was achieved in 80.4%, with 1- and 3-year OS rates of 68.5% and 39.0%, respectively (122). The common/proper hepatic artery is sometimes involved right at

the emergence of the gastroduodenal artery. This can be resected selectively with end-to-end reconstruction or graft interposition, as demonstrated by Amano et al (123). The SMA has been very, very rarely resected in cases of PDAC, which has been demonstrated to incur high perioperative morbidity and mortality in a recent meta-analysis (124).

Based on data using neoadjuvant chemotherapy and RT, different consensus guidelines have supported surgical exploration of BR patients amenable to reconstruction after a course of neoadjuvant therapy, good performance status, and the absence of metastatic disease (17, 20, 30). However, no consensus has been reached regarding the ideal timing for exploratory laparotomy after neoadjuvant therapy completion for BR patients. Takai et al (33) reported that surgical resection in their series was performed 3 to 4 weeks after neoadjuvant therapy completion. In contrast, in the large series reported by Katz et al (57), the median interval from the completion of neoadjuvant therapy to surgery was 7 weeks (range 2-51). However, in the recently opened phase III trial testing preoperative chemoradiation versus immediate surgery for resectable and BR pancreatic cancer (PREOPANC trial; EU Clinical Trials Register no. 2012-003181-40), exploratory laparotomy will be performed 14 and 18 weeks after randomization, usually $\geq$4 weeks after chemoradiation completion (125).

Surgical margin definition

At present, what constitutes a clear surgical margin has not been standardized. Some groups have defined R0 resection as no microscopic evidence of tumor at the edge of the inked specimen (126), and others have required the tumor to be >1 mm from the inked margin (127, 128). The lack of agreement on margin definition and variation in pathologic techniques have created heterogeneity when comparing outcomes. This discrepancy has been shown to have clinical and prognostic implications (129). Varying clear margin definitions significantly affected the rates of R0 resection in pancreatic cancer surgery in one study, with an R0 rate of 72% if defined as tumor free from the inked edge versus 49% if defined as tumor >1 mm from the inked edge (130). A retrospective analysis of resected pancreatic cancer showed that cases with tumor at the margin had a median OS of 12.6 months compared with 15.4 months for tumors within 1 mm from the margin and 25.4 months for those with tumor >1 mm from the margin (131). Currently, the NCCN does not provide a clear margin definition for PDAC but has recommended that information regarding the distance of tumor from the specimen edge be stated in millimeters for all cases. Taken together, these data highlight the necessity for a standardized definition for the specimen margin in PDAC (17).

Intraoperative RT

IORT has been widely studied for pancreatic cancer owing to the complex anatomy of the region and, consequently, high risk of positive resection margins. The margin status can be determined intraoperatively using frozen tissue pathologic examination. It has the advantage of offering high radiation doses to the resection bed, while sparing adjacent normal tissues, which could be appropriate for BR disease.

Most of the experience with IORT is retrospective, demonstrating improved local control and symptomatic control but usually without significant improvement in OS (132-136). Ashman et al (137) reported a series of 11 borderline and 20 unresectable PDAC patients who underwent neoadjuvant chemoradiation followed by resection and IORT. The dose was determined by both the extent of resection and the dose of preoperative external beam RT: for the patients with R0 resection, 12.5 Gy; R1, median 12.5 Gy (range 10-15); R2, 15 Gy; and unresectable 17.5 Gy (n = 2) or 20 Gy (n = 12). The median survival for the entire group of 31 patients was 19 months, with a 2-year OS of 31% and 16% rate of local failure (137).

A multicenter series from Japan included 210 resected cases of PDAC that received IORT (138). The R0 and R1 resection rates were 70% and 30%, respectively. The IORT median dose was 25 Gy (range 20-30). Local failure was observed in only 31 patients (14.8%), with a 2-year local control rate of 87.1% for R0 and 74.6% for R1 resections. The dose of IORT did not affect local control.

Another retrospective study included 46 PDAC patients who underwent resection, of whom 21 received IORT and adjuvant RT. IORT was an independent prognostic factor for OS ($P < .01$) and local control ($P = .03$) on multivariate analysis, despite overall poor 5-year survival (13%) and local control (46%) rates (139).

Investigators from the Massachusetts General Hospital reported on the outcomes of locally advanced (n = 60) and BR (n = 8) PDAC patients who underwent neoadjuvant chemotherapy and chemoradiation, followed by surgical exploration and IORT. The median external beam RT dose was 50.4 Gy (range 24-55). A median IORT dose of 10 Gy was delivered to the resection bed and positive surgical margins, and a median of 15 Gy was delivered to unresectable tumors. Ultimately, 41 patients (60%) were able to undergo resection. The median OS was 24.5 months for the resected patients and 35.1 months for those who received IORT in addition to resection (P = NS), without an increase in toxicity (140).

The favorable local control rates reported indicate that IORT could have a role in BR disease. However, because of the lack of randomized data demonstrating benefit, the use of IORT should be reserved for highly selected cases treated at specialized centers (141).

Discussion

A clear rationale exists to offer neoadjuvant therapy to patients with BR pancreatic cancer to downstage disease and facilitate clear resection margins. However, the optimal

neoadjuvant treatment regimen has not been determined. Several phase II prospective studies and retrospective institutional series exploring different sequences and combinations of chemotherapy and RT have been reported. However, no comparison between regimens has been conducted in a randomized phase III trial. The heterogeneity of treatment regimens used among the different studies made it difficult to derive definitive conclusions regarding superiority of any single approach.

From the data extrapolated from studies of locally advanced PDAC, one common strategy has been to offer RT combined with radiosensitizing chemotherapy. The radiation doses used for BR cases are similar to doses used for definitive treatment of locally advanced disease, ranging from 45 to 50.4 Gy when conventionally fractionated schedules are used or 30 Gy in 10 fractions as reported from the MDACC institutional experience. As previously demonstrated, the resection rates and histologic treatment response after neoadjuvant regimens that included RT appeared to be greater compared with neoadjuvant chemotherapy alone, despite no differences in survival rates (32, 33, 40, 42, 44, 50). Even for patients whose cases ultimately are not amenable to tumor resection, the greater rates of local tumor control with the addition of RT has been shown to improve symptoms and quality of life (142).

Different chemotherapy agents have been investigated as radiation sensitizers during preoperative chemoradiation. Despite the inherent design differences, studies using gemcitabine or gemcitabine-based drug combinations concurrent with RT appear to result in greater rates of tumor resectability (range 39%-87%) compared with fluoropyrimidine-based concurrent regimens (range 23%-68%), although at the cost of greater toxicity and worse quality of life (143).

A promising approach has been to offer induction systemic therapy with the objective of targeting microscopic systemic disease and selecting out patients with early onset of metastatic progression, sparing these patients from the toxicities of aggressive local therapies. Patients without systemic progression on reassessment after induction chemotherapy could immediately undergo surgery or receive local therapy using chemoradiation or SBRT to maximize tumor downstaging and margin sterilization before attempting resection. The encouraging outcomes obtained with induction FOLFIRINOX and gemcitabine plus nab-paclitaxel reinforce the rationale behind starting with induction chemotherapy, followed by RT, as a standard neoadjuvant regimen. A proposed algorithm is provided in Figure 4.

Improvements in the image guidance systems, coupled with the development of subcentimeter multileaf collimators and 6-dimensional robotic tables allows for greater precision with patient setup and compensating for inter- and intrafraction target motion, enabling the expansion of SBRT. This RT modality offers a greater biologically equivalent dose, greater target precision, and a shorter treatment delivery time, usually 1 to 5 days, compared with 4 to 5 weeks for conventionally fractionated RT, reducing the interval that the patient remains without systemic therapy. Excellent local control rates have been achieved with SBRT for locally advanced PDAC. Similarly, these results have been observed in studies using SBRT for BR disease, especially for patients without systemic progression after induction chemotherapy (81-87).

Despite an appropriate and thorough radiologic assessment that currently guides therapeutic approaches, it has been demonstrated that other factors such as tumor genetics and the local microenvironment also play important roles in the natural history of pancreatic adenocarcinoma (94, 144, 145). Combining information from all these features is necessary to improve treatment strategies and offer patients the best chance of cure, while preserving them from unnecessary toxicities.

Conclusions

Despite the controversies regarding the optimal method to define BR disease, a consensus is growing that this subset of PDAC represents a unique class within the spectrum of PDAC, with its own prognosis, which can be significantly improved if a favorable response is achieved after preoperative therapy and resection. Evolving techniques of surgery could also increase the number of patients who might be considered to have BR disease. Prospective randomized trials comparing different neoadjuvant regimens are needed to properly define the best neoadjuvant treatment regimen before surgery.

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